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# Incidence and Prognostic Significance of Depressive Symptoms in Peripheral Artery Disease

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**Background**—We compared the incidence of depression, defined by a Geriatric Depression Score (GDS)  $\geq 6$ , between people with versus without peripheral artery disease (PAD). We determined whether depressive symptoms were associated with increased mortality in people with and without PAD.

**Methods and Results**—Nine hundred and fifty-one PAD patients and 478 non-PAD patients were recruited from Chicago medical centers and followed prospectively. At baseline and annually, participants completed the GDS (0–15 scale, score  $\geq 6$ =depression) and 6-minute walk. Cause of death was confirmed with death certificates. The prevalence of a GDS  $\geq 6$  at baseline was 186/951 (19.6%) among PAD versus 63/478 (13.2%) among non-PAD participants ( $P=0.003$ ). During a mean follow-up of  $2.7 \pm 1.2$  years, 122/712 (17.1%) of participants with PAD versus 51/403 (12.7%) without PAD developed a GDS  $\geq 6$  ( $P=0.047$ ). Adjusting for age, sex, race, comorbidities, and other confounders, PAD participants had an increased rate of developing a GDS  $\geq 6$  compared to non-PAD participants (hazard ratio=1.54 (95% CI=1.05–2.25,  $P=0.026$ ). This association was not statistically significant after adjusting for 6-minute walk ( $P=0.258$ ). Among PAD participants, a baseline GDS  $\geq 6$  was associated with increased all-cause mortality, adjusting for confounders (hazard ratio=1.57, 95% CI=1.12–2.21,  $P=0.009$ ). This association was not significant after adjusting for 6-minute walk ( $P=0.224$ ).

**Conclusions**—People with PAD have a higher incidence of depressive symptoms than people without PAD. In PAD, depressive symptoms are associated with increased all-cause and cardiovascular mortality. These associations are explained in part by poorer 6-minute walk among people with PAD and among depressed people with PAD, respectively. (*J Am Heart Assoc.* 2016;5:e002959 doi: 10.1161/JAHA.115.002959)

**Key Words:** atherosclerosis • cardiovascular disease • peripheral vascular disease

The incidence and prognostic significance of depression in people with lower extremity peripheral artery disease (PAD) are unclear. Cross-sectional studies report a higher prevalence of depression or depressive symptoms among people with PAD compared to those without PAD.<sup>1–3</sup>

However, to our knowledge, no prospective studies have compared the incidence of depression or new depressive symptoms among people with PAD compared to those without PAD. Among patients with coronary artery disease, individuals with depression have higher morbidity and mortality rates than people without depression.<sup>4,5</sup> One prior study reported that among symptomatic patients undergoing lower extremity revascularization, those with depression had a higher risk of the combined outcome of death or major adverse cardiovascular events than those without depression.<sup>6</sup> However, the association of depression with mortality among PAD patients, including those not planning revascularization, has not been studied previously to our knowledge.

To determine whether patients with PAD have an increased incidence of depressive symptoms compared to people without PAD, we compared rates of new onset of depressive symptoms over time between people with versus without PAD. We hypothesized that people with PAD would have a higher incidence of depressive symptoms compared to people without PAD. To determine whether depressive

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symptoms are associated with increased all-cause and cardiovascular disease (CVD) mortality in people with PAD, we compared mortality rates between people with versus without depressive symptoms. We hypothesized that among people with PAD, those with depressive symptoms would have a higher mortality rate than those without depressive symptoms.

## Methods

### Study Overview

We combined data from 3 prospective observational studies of patients with PAD: The Walking and Leg Circulation Study (WALCS), WALCS II, and WALCS III cohorts.<sup>7–10</sup> WALCS was conducted between 1998 and 2002,<sup>7,8</sup> WALCS II was conducted between 2002 and 2006, and WALCS III between 2005 and 2014.<sup>9,10</sup> In all 3 studies, PAD participants were recruited from among consecutively identified PAD patients at Chicago-area medical centers and followed longitudinally. The institutional review boards of Northwestern University and all participating medical centers approved the protocol for the 3 studies. All participants gave written informed consent. In each study, participants completed baseline testing and returned annually for follow-up for up to 4 years. In the WALCS cohort, all participants were age 55 and older at baseline. In WALCS II, all participants were age 59 and older at baseline. In WALCS III, there were no age restrictions.

### Participant Identification

Similar recruitment methods were used for all 3 studies.<sup>7–10</sup> In all 3 cohorts, PAD participants were identified from among consecutive patients with PAD in Chicago-area vascular surgery and noninvasive vascular laboratories.<sup>7–10</sup> Participants were also identified from among lists of consecutive PAD patients in cardiology, general medicine, endocrinology, and geriatric clinics at Northwestern. In the WALCS and WALCS II cohorts, participants without PAD were identified from among consecutive patients in a general internal medicine practice who were screened with the ankle-brachial index (ABI) and found to have an ABI of 0.90 to 1.50. In the WALCS III cohort, participants without PAD were identified (from among consecutive patients age 65 and older in Northwestern's general internal medicine practice) who had no history of smoking, diabetes mellitus, or established cardiovascular disease, including PAD. In addition, participants without PAD in WALCS I and WALCS II were identified (from among consecutive patients in a noninvasive vascular laboratory without PAD) who had an ABI of 0.90 to 1.50 at their baseline study visit.

### Inclusion Criterion

All PAD participants in these analyses had a baseline ABI value of  $<0.90$ .<sup>11</sup> All non-PAD participants included in these analyses had a baseline ABI of 0.90 to 1.30.<sup>11</sup>

### Exclusion Criteria

In all 3 studies, patients with dementia were excluded because of their inability to answer questions accurately. Nursing home residents were excluded because they had severely impaired functioning at baseline. Non-English-speaking patients were excluded because investigators were not fluent in non-English languages. Patients with recent major surgery were excluded because the surgery may have influenced their walking speed, sitting down time, or lying down time. Potential participants who were wheelchair bound or who had a history of leg or foot amputations were excluded because of their severe functional impairment at baseline. In the WALCS III cohort, participants with contraindications to magnetic resonance imaging testing were excluded. Participants with critical limb ischemia were not included in any cohorts.

### ABI Measurement

A hand-held Doppler probe (Nicolet Vascular Pocket Dop II; Nicolet Biomedical Inc, Golden, CO) was used to measure systolic pressures in the right and left brachial, dorsalis pedis, and posterior tibial arteries.<sup>11,12</sup> Each pressure was measured twice. For each leg, the ABI was calculated by dividing the mean of the dorsalis pedis and posterior tibial pressures by the mean of the 4 brachial pressures.<sup>13</sup> Average brachial pressures in the arm with highest pressure were used when one brachial pressure was higher than the opposite brachial pressure in both measurement sets and the 2 brachial pressures differed by 10 mm Hg or more in at least 1 measurement set. In these cases, subclavian stenosis was possible.<sup>13</sup> The leg with lowest ABI was used in analyses.

### Depressive Symptoms

Depressive symptoms were measured at baseline and at annual follow-up visits with the Geriatric Depression Scale Short Form (GDS-S).<sup>14–17</sup> The GDS-S is a well-validated 15-item questionnaire, derived from the Center for Epidemiological Studies Depression scale, which measures the number of depressive symptoms. Scores range from 0 to 15 (15=worst score).<sup>14–18</sup> A GDS-S score  $\geq 6$  is 92% sensitive and 81% specific for clinical depression, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R).<sup>14</sup> “The GDS-S improves in response to a

therapeutic intervention and changes in the GDS-S are associated with temporally corresponding changes in the ability to perform Activities of Daily Living and Instrumental Activities of Daily Living.<sup>19,20</sup>

## Six-Minute Walk

The 6-minute walk test was performed at baseline using a standardized and well-validated protocol.<sup>21,22</sup> Participants walked up and down a 100-foot hallway for 6 minutes after instructions to cover as much distance as possible.

## Comorbidities

Comorbidities assessed at baseline were diabetes, angina, myocardial infarction, heart failure, cancer, chronic lung disease, and stroke. Disease-specific algorithms that combine data from patient report, medical record review, medications, laboratory values, and a questionnaire completed by the participant's primary care physician were used to verify and document baseline comorbidities.<sup>23</sup>

## Medications

Participants were asked to bring their medication bottles or a complete list of their medications to their baseline study visit. Names of each medication were recorded. The study principal investigator (M.M.M.) reviewed each medication, blinded to other characteristics, and indicated whether the medication was a statin, angiotensin-converting enzyme inhibitor, or antiplatelet therapy.

## Income

We used participants' zip code linked to US census data to categorize participants according to the median annual household income in their zip code.<sup>24</sup>

## Education Level

Participants were asked their highest level of education achieved, using a questionnaire administered by trained and certified interviewers.

## Mortality Assessment

At baseline, participants provided names of 3 proxies to assist with ascertaining complete follow-up. Mortality information was obtained from family members, proxies, and primary care physicians. For patients lost to follow-up, we used the Social Security Administration death database to search for deaths. Death certificates were obtained from the State of Illinois or

from medical records. Cardiovascular disease deaths consisted of deaths due to coronary heart disease, stroke, peripheral vascular disease, and other cardiovascular disease. The date of death was obtained from the death certificate. Follow-up for participants who were not deceased continued until the date of last contact at a study visit or by telephone.

## Statistical Analyses

Two-sample *t* tests and  $\chi^2$  tests were used to compare continuous and binary baseline clinical characteristics, respectively, according to the presence versus absence of PAD and according to the presence versus absence of depression at baseline. Two-sample *t* tests and  $\chi^2$  analyses were also used to compare baseline characteristics of participants without depression at baseline who developed depression during follow-up versus those who did not develop depression during follow-up among PAD and non-PAD subgroups separately. We used Kaplan–Meier curves and log-rank analyses to compare cumulative probabilities of depression among participants with versus without PAD at baseline. Among participants with and without PAD at baseline, we used Kaplan–Meier curves and log-rank analyses to compare cumulative probabilities of all-cause mortality between participants with versus without depression at baseline.

In our primary analyses, Cox regression models were used to establish the association of PAD with development of depression during follow-up, stratifying by study cohort (WALCS I, WALCS II, or WALCS III), and adjusting for age, sex, race, body mass index (BMI), smoking, comorbidities, income, and education. In secondary analyses, we repeated analyses with additional adjustment for baseline 6-minute walk. We imputed income and/or education for 22 participants missing data on income or education, using the cohort median for imputation.

Cox regression models were used to evaluate the association of baseline characteristics with development of depression during follow-up among participants with and without PAD, stratifying by study cohort, and adjusting for age, sex, race, 6-minute walk, BMI, smoking, comorbidities, ABI, income, and education.

In our primary analyses, Cox regression models were used to establish the association of depression at baseline with all-cause mortality and with cardiovascular disease mortality among participants with and without PAD, respectively, stratifying by study cohort, and adjusting for age, sex, race, BMI, smoking, comorbidities, medications, income, education level, and ABI. In secondary analyses, we repeated analyses with additional adjustment for baseline 6-minute walk. We tested for an interaction of study cohort with the associations in our primary analyses.

In post-hoc, exploratory analyses, we analyzed whether greater decline in the 6-minute walk and whether greater declines in the ABI were each associated with a higher incidence of subsequent depression in participants with and without PAD, respectively, using Cox proportional hazards analyses. In these analyses we stratified participants with and without PAD according to their degree of decline in the 6-minute walk and their decline in the ABI during the first 2 years of follow-up and related each independent variable of interest to the subsequent incidence of depression, adjusting for confounders.

Analyses were performed using SAS statistical software (version 9.4, SAS Institute Inc, Cary, NC).

## Results

Among 1074 individual participants with PAD enrolled in the WALCS I, WALCS II, and WALCS III cohorts, 29 were lost to follow-up, 67 did not complete the GDS-S form at baseline, and 27 were missing covariate data required for analyses (Figure 1). Among 532 individual participants without PAD, 16 were lost to follow-up, 26 did not complete the GDS-S form at baseline, and 12 were missing covariate data. The remaining 951 participants with PAD and 478 without PAD were included in analyses.

### Characteristics of Participants at Baseline

Overall, participants with PAD were older and had lower BMI and ABI values compared to participants without PAD (Table 1). Participants with PAD included a higher proportion of men and had higher prevalences of current smoking, diabetes, angina, heart failure, prior myocardial infarction, and stroke, compared to people without PAD (Table 1). Participants with PAD had poorer 6-minute walk performance at baseline and a lower baseline prevalence of spinal stenosis compared to people without PAD. Participants with PAD had higher prevalences of using statins, anti-platelet therapy, or angiotensin-converting enzyme inhibitors than those without PAD.

At baseline, 186/951 (19.6%) of participants with PAD met criteria for depression versus 63/478 (13.2%) of those without PAD ( $P=0.003$ ). Table 1 shows characteristics associated with presence versus absence of PAD and presence versus absence of depression at baseline. Among participants with PAD, those depressed at baseline were younger, included a higher prevalence of current smokers, and included higher prevalences of African Americans and people with pulmonary disease, diabetes, history of stroke, heart failure, hip arthritis, disk disease, and spinal stenosis (Table 1). PAD participants with depression at baseline had poorer 6-minute walk performance, a lower prevalence of cancer, achieved less

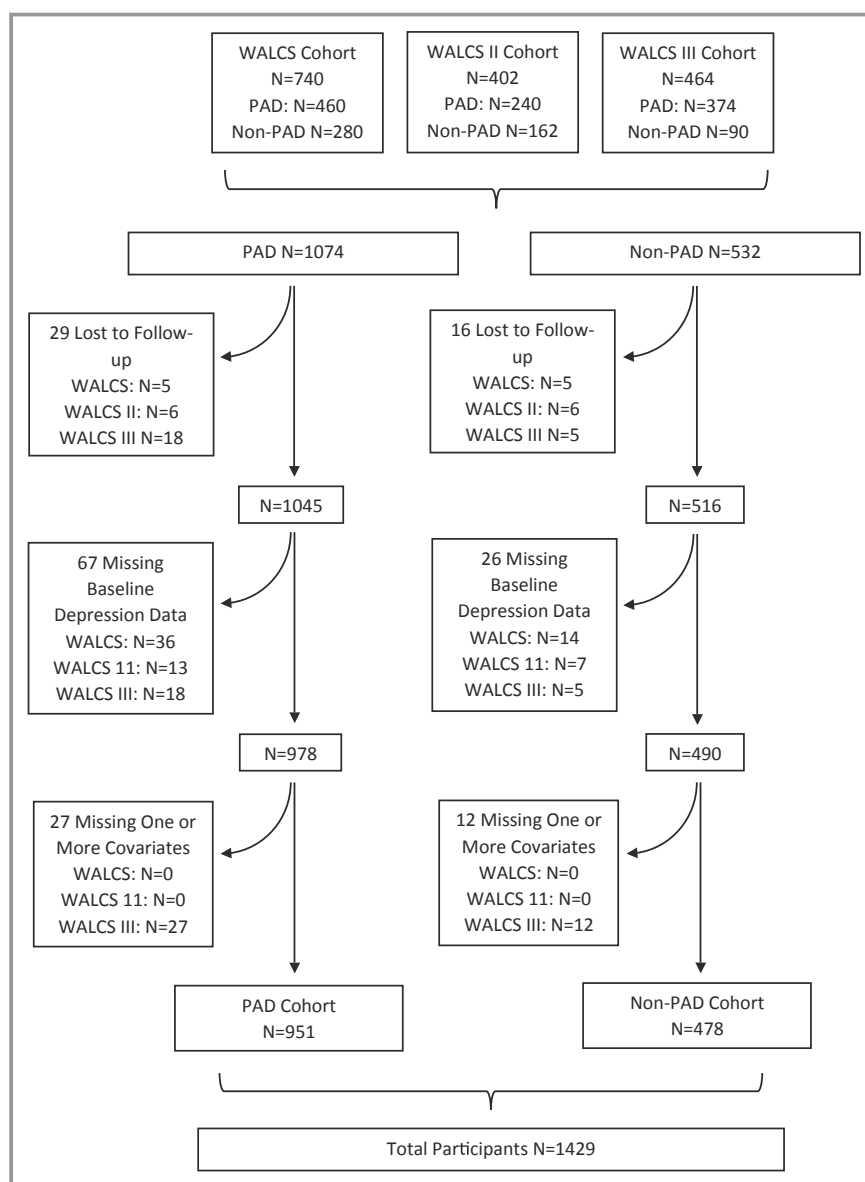
education, and lived in a zip code with lower median income than PAD participants without depression at baseline (Table 1). Participants without PAD who were depressed at baseline had higher prevalences of current smoking, diabetes, angina, and heart failure compared to participants without PAD who were not depressed. Participants without PAD who were depressed at baseline had poorer 6-minute walk performance and had achieved lower levels of education than those not depressed at baseline (Table 1).

### Incidence of Depression During Follow-Up in People With Versus Without PAD

Among all participants without depression at baseline, the incidence of depression, measured by newly developing a GDS  $\geq 6$  after baseline, was 122/712 (17.1%) among participants with PAD and 51/403 (12.7%) among participants without PAD during a mean follow-up of  $2.7 \pm 1.2$  years. The cumulative probability of developing new depression during follow-up between participants with versus without PAD at baseline is shown in Figure 2 (log-rank test  $P=0.0026$ ). There was no association of PAD severity with incidence of depression (ABI  $<0.50$ : 21/125 [16.8%], ABI 0.50 to  $<0.90$ : 101/587 [17.2%]; ABI 0.90–1.30: 51/403 [12.7%],  $P=0.139$ ). Among women, the incidence of depression was 53/279 (19.0%) among participants with PAD versus 29/221 (13.1%) among those without PAD. Among men, the incidence of PAD was 69/433 (15.9%) among those with PAD versus 22/182 (12.1%) among those without PAD. Among participants age  $>75$ , the incidence of depression was 47/254 (18.5%) among participants with PAD and 13/91 (14.3%) among participants without PAD. Among participants age  $\leq 75$  years, the incidence of depression was 75/458 (16.4%) among those with PAD and 38/312 (12.2%) among those without PAD. Therefore, the higher incidence of depression among people with PAD compared to those without PAD was consistent among men and women and in older and younger participants. There was no interaction of study cohort with the analyses assessed in our primary analyses (data not shown).

In analyses stratifying by study cohort, and adjusting for age, sex, race, BMI, smoking, comorbidities, education, and income, PAD was associated with a higher risk of developing new depression compared to people without PAD (hazard ratio [HR]=1.54, 95% CI=1.05–2.25,  $P=0.026$ ). However, this association was no longer statistically significant when the analyses were additionally adjusted for baseline 6-minute walk performance (HR=1.26, 95% CI=0.85–1.86,  $P=0.258$ ).

Among PAD participants, current smoking, heart failure, knee arthritis, and 6-minute walk were each associated independently with risk of developing depression during follow-up (Table 2), in stratified analyses adjusting for age,



**Figure 1.** Summary of included participants from the Walking and Leg Circulation Study (WALCS), WALCS II, and WALCS III cohorts. PAD indicates peripheral artery disease.

sex, race, BMI, comorbidities, ABI, income, and education level. In a similar multivariable analysis among participants without PAD, only 6-minute walk performance was associated with developing depression during follow-up (Table 2).

PAD participants with depression at baseline had higher all-cause mortality rates during follow-up compared to PAD participants without depression at baseline (54/186 [29.0%] versus 153/765 [20.0%]). The cumulative probability of all-cause mortality between PAD participants with versus without depression at baseline is shown in Figure 3A (log-rank test  $P=0.005$ ). In multivariable analyses, depression at baseline was associated with higher all-cause mortality, stratifying by study cohort, and adjusting for age, sex, race, comorbidities,

ABI, smoking, BMI, medication use, income, and education level (HR=1.57, 95% CI=1.12–2.21,  $P=0.009$ ) among people with PAD (Table 3). However, this association was not statistically significant after additional adjustment for 6-minute walk (HR=1.25, 95% CI=0.87–1.79,  $P=0.224$ ). In multivariable analyses, depression at baseline was associated with higher cardiovascular disease mortality, stratifying by study cohort, and adjusting for age, sex, race, comorbidities, ABI, smoking, BMI, medication use, income, and education (HR=1.80, 95% CI=1.03–3.13,  $P=0.038$ ) (Table 3) among people with PAD. However, this association was not statistically significant after additional adjustment for 6-minute walk (HR=1.38, 95% CI=0.77–2.46,  $P=0.277$ ) (Table 3).



**Table 1.** Participant Characteristics According to Presence Versus Absence of PAD and Depression

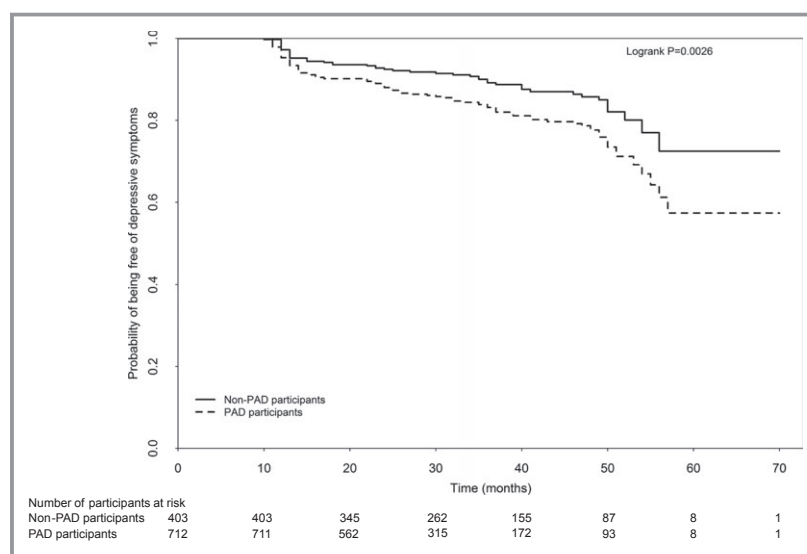
Group	PAD		People Without PAD					P Value <sup>†</sup>	P Value <sup>‡</sup>	P Value <sup>§</sup>
	All PAD Participants (N=951)	With Depression at Baseline (N=186)	Without Depression at Baseline (N=765)	P Value*	All Participants Without PAD (N=478)	With Depression at Baseline (N=63)	Without Depression at Baseline (N=415)			
Age, y	71.29 (9.14)	68.62 (9.56)	71.94 (8.93)	<0.001	69.70 (7.71)	70.25 (8.79)	69.61 (7.54)	0.539	0.001	
Body mass index, kg/m <sup>2</sup>	28.21 (5.40)	28.67 (6.09)	28.10 (5.21)	0.201	29.11 (6.20)	30.00 (7.13)	28.97 (6.04)	0.221	0.005	
Ankle-brachial index	0.64 (0.15)	0.64 (0.16)	0.65 (0.15)	0.704	1.08 (0.11)	1.06 (0.12)	1.08 (0.10)	0.152	<0.001	
Men (%)	61.1, N=581	62.4, N=116	60.8, N=465	0.692	46.2, N=221	52.4, N=33	45.3, N=188	0.294	<0.001	
African American (%)	22.9, N=218	28.5, N=53	21.6, N=165	0.044	20.1, N=96	25.4, N=16	19.3, N=80	0.259	0.221	
Current smoker (%)	21.1, N=201	33.9, N=63	18.0, N=138	<0.001	7.9, N=38	15.9, N=10	6.7, N=28	0.013	<0.001	
Diabetes (%)	34.3, N=326	41.9, N=78	32.4, N=248	0.014	20.9, N=100	33.3, N=21	19.0, N=79	0.009	<0.001	
Pulmonary disease (%)	36.5, N=347	50.0, N=93	33.2, N=254	<0.001	32.4, N=155	42.9, N=27	30.8, N=128	0.058	0.129	
Cancer (%)	16.8, N=16	10.8, N=20	18.3, N=140	0.014	17.8, N=85	25.4, N=16	16.6, N=69	0.09	0.65	
Angina (%)	29.0, N=276	32.3, N=60	28.2, N=216	0.278	19.7, N=94	36.5, N=23	17.1, N=71	<0.001	<0.001	
Myocardial infarction (%)	23.4, N=223	26.9, N=50	22.6, N=173	0.218	13.4, N=64	17.5, N=11	12.8, N=53	0.308	<0.001	
Stroke (%)	15.2, N=145	23.1, N=43	13.3, N=102	<0.001	5.6, N=27	11.1, N=7	4.8, N=20	0.07	<0.001	
Heart failure (%)	19.8, N=188	31.2, N=58	17.0, N=130	<0.001	12.1, N=58	20.6, N=13	10.8, N=45	0.027	<0.001	
Hip arthritis (%)	3.2, N=30	8.6, N=16	1.8, N=14	<0.001	2.5, N=12	1.6, N=1	2.7, N=11	1	0.496	
Knee arthritis (%)	9.8, N=93	12.4, N=23	9.2, N=70	0.185	12.3, N=59	20.6, N=13	11.1, N=46	0.032	0.138	
Disk disease (%)	31.3, N=298	39.8, N=74	29.3, N=224	0.006	31.4, N=150	33.3, N=21	31.1, N=129	0.72	0.986	
Spinal stenosis (%)	10.1, N=96	14.5, N=27	9.0, N=69	0.026	34.1, N=163	42.9, N=27	32.8, N=136	0.116	<0.001	
Six-minute walk (feet)	1127.66 (388.38)	918.11 (389.38)	1178.61 (370.89)	<0.001	1422.27 (399.67)	1237.76 (465.44)	1450.28 (381.62)	<0.001	<0.001	
Median annual household income (US dollars)	53 186 (20 496)	50 283 (22 019)	53 892 (20 059)	0.031	54 871 (21 362)	52 775 (17 306)	55 189 (21 913)	0.404	0.149	
Less than high school (%)	10.94, N=104	17.20, N=32	9.41, N=72	0.005	9.83, N=47	20.63, N=13	8.19, N=34	0.008	0.013	
High school to college (%)	69.93, N=665	67.74, N=126	70.46, N=539		64.23, N=307	55.56, N=35	65.54, N=272			
Graduate school (%)	19.14, N=182	15.05, N=28	20.13, N=154		25.94, N=124	23.81, N=15	26.27, N=109			
Medication use										
Statin use (%)	54.9, N=522	54.8, N=102	54.9, N=420	0.988	32.8, N=157	33.3, N=21	32.8, N=136	0.929	<0.001	
ACE inhibitor use (%)	33.9, N=322	34.4, N=64	33.7, N=258	0.860	23.6, N=113	27.0, N=17	23.1, N=96	0.503	<0.001	
Anti-platelet use (%)	64.8, N=616	64.0, N=119	65.0, N=497	0.800	42.5, N=203	44.4, N=28	42.2, N=175	0.733	<0.001	

Values shown are means (SD). ACE indicates angiotensin-converting enzyme; PAD, peripheral artery disease.

\*P value compares characteristics between participants with depression and those without depression among participants with PAD.

†P value compares characteristics between participants with depression and those without depression among participants without PAD.

‡P value compared characteristics between participants with peripheral artery disease and those without. Depression at baseline was defined based on a Geriatric Depression Scale score  $\geq 6$  at baseline.



**Figure 2.** Association of baseline peripheral artery disease status with new onset of depressive symptoms among people without depressive symptoms at baseline.

**Table 2.** Multivariable Analyses of Baseline Characteristics Associated With Development of Depression During Follow-Up Among Participants With and Without PAD

	Participants With PAD (N=712)		Participants Without PAD (N=403)	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Age, y	1.01 (0.98–1.03)	0.638	0.98 (0.94–1.02)	0.320
Male sex	0.87 (0.59–1.30)	0.502	1.10 (0.58–2.09)	0.777
African American race	0.66 (0.38–1.14)	0.136	0.56 (0.23–1.34)	0.190
Six-minute walk (feet) baseline (hazard ratio calculated per 100 feet)	0.94 (0.89–1.00)	0.047	0.86 (0.79–0.93)	<0.001
Body mass index, kg/m <sup>2</sup>	0.98 (0.95–1.02)	0.413	1.02 (0.97–1.07)	0.458
Current smoker	1.94 (1.21–3.12)	0.006	1.12 (0.26–4.82)	0.879
Diabetes	1.12 (0.74–1.71)	0.581	1.36 (0.62–2.96)	0.441
Pulmonary disease	1.05 (0.71–1.55)	0.817	1.29 (0.69–2.43)	0.426
Cancer	1.45 (0.91–2.31)	0.119	0.82 (0.33–2.07)	0.678
Angina	1.28 (0.82–1.98)	0.273	1.55 (0.66–3.66)	0.318
Myocardial infarction	1.05 (0.67–1.67)	0.822	1.14 (0.45–2.90)	0.782
Stroke	1.00 (0.58–1.72)	0.994	0.70 (0.16–3.11)	0.637
Heart failure	1.66 (1.04–2.66)	0.034	0.97 (0.41–2.30)	0.946
Hip arthritis	1.31 (0.44–3.91)	0.623	2.12 (0.54–8.39)	0.284
Knee arthritis	2.26 (1.35–3.77)	0.002	1.80 (0.79–4.14)	0.163
Disk disease	1.09 (0.72–1.65)	0.673	0.89 (0.48–1.68)	0.724
Spinal stenosis	1.46 (0.82–2.59)	0.194	1.42 (0.77–2.63)	0.258
Ankle brachial index	1.62 (0.42–6.24)	0.483	1.17 (0.06–24.31)	0.917
Median annual household income ≤\$51 249 vs median annual household income >\$51 249	0.88 (0.59–1.31)	0.530	0.50 (0.26–0.99)	0.046
Less than high school vs graduate school	1.81 (0.90–3.65)	0.096	1.48 (0.49–4.53)	0.489
High school to college vs graduate school	1.17 (0.72–1.91)	0.535	0.86 (0.42–1.78)	0.691

PAD indicates peripheral artery disease.



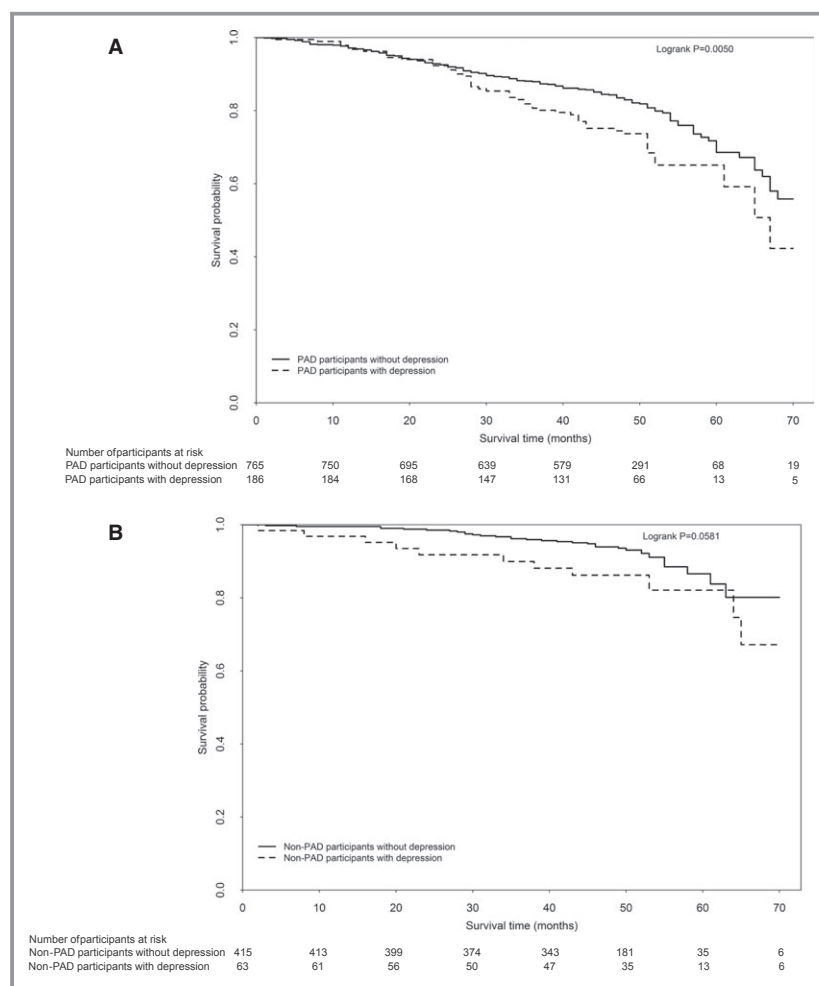
Among participants without PAD, there was no difference in the cumulative probability of all-cause mortality among those with versus without depression at baseline (Figure 3B). Among participants without PAD, there was no difference in all-cause or cardiovascular disease mortality among those depressed at baseline compared to those not depressed at baseline, stratifying by study cohort, and adjusting for age, sex, race, comorbidities, ABI, smoking, BMI, education level, income, and medications (HRs=1.32 [95% CI 0.57–3.06] and 0.85 [95% CI 0.14–5.12] respectively). There were no significant interactions of presence versus absence of PAD with the association of depression and all-cause or cardiovascular mortality ( $P=0.909$  and  $0.374$ , respectively).

Among participants with PAD, an ABI decline  $>0.15$  or a greater decline in the 6-minute walk during the first 2 years of follow-up, respectively, were not associated with a higher subsequent incidence of depression, adjusting for age, sex, race, comorbidities, smoking, BMI, baseline ABI, baseline 6-minute walk, income, or education (Tables 4 and 5, respec-

tively). Among participants without PAD, ABI declines  $>0.15$  and greater declines in the 6-minute walk, respectively, were associated with greater subsequent risk of depression, adjusting for age, sex, race, comorbidities, smoking, BMI, baseline ABI, baseline 6-minute walk, income, or education (Tables 4 and 5, respectively).

## Discussion

Among 951 participants with PAD and 478 without PAD, we report new findings regarding the incidence and clinical significance of depressive symptoms in people with PAD. First, people with PAD had a higher prevalence of depression at baseline and a higher rate of developing new depression during follow-up compared to people without PAD. The association of PAD with developing new depression was independent of age, sex, race, smoking, BMI, comorbidities, education, and income. However, the association of PAD with increased risk of depressive symptoms was no longer



**Figure 3.** A, Association of depressive symptoms with all-cause mortality in participants with peripheral artery disease (N=951); (B) Association of depressive symptoms with all-cause mortality in participants without peripheral artery disease (N=478).

**Table 3.** Adjusted Associations of Depression at Baseline With All-Cause and Cardiovascular Disease Mortality Among Participants With PAD (N=951)

	All-Cause Mortality		Cardiovascular Disease Mortality	
	Adjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio With Adjustment for 6-Minute Walk (95% CI)	Adjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio With Adjustment for 6-Minute Walk (95% CI)
Depressed at baseline	1.57 (1.12–2.21)	1.25 (0.87–1.79)	1.80 (1.03–3.13)	1.38 (0.77–2.46)
Age, y	1.04 (1.02–1.06)	1.03 (1.01–1.05)	1.06 (1.03–1.09)	1.05 (1.01–1.08)
Male sex	1.52 (1.12–2.07)	1.73 (1.27–2.37)	1.51 (0.90–2.54)	1.85 (1.08–3.16)
African American race	0.85 (0.58–1.25)	0.79 (0.53–1.17)	0.99 (0.52–1.88)	0.91 (0.48–1.74)
Body mass index, kg/m <sup>2</sup>	0.96 (0.93–0.99)	0.95 (0.92–0.98)	0.97 (0.92–1.02)	0.95 (0.90–1.01)
Current smoker	1.00 (0.68–1.47)	0.96 (0.65–1.41)	1.35 (0.72–2.55)	1.29 (0.68–2.44)
Diabetes	1.24 (0.91–1.69)	1.17 (0.86–1.60)	1.28 (0.77–2.14)	1.16 (0.69–1.94)
Pulmonary disease	1.20 (0.90–1.62)	1.09 (0.81–1.48)	1.09 (0.66–1.79)	0.97 (0.58–1.62)
Cancer	1.78 (1.28–2.48)	1.73 (1.24–2.42)	0.77 (0.39–1.55)	0.72 (0.36–1.46)
Angina	1.14 (0.82–1.59)	1.11 (0.80–1.55)	1.74 (1.02–2.96)	1.71 (1.00–2.93)
Myocardial infarction	0.91 (0.64–1.29)	0.90 (0.64–1.28)	0.84 (0.47–1.52)	0.84 (0.47–1.51)
Stroke	1.16 (0.80–1.69)	1.02 (0.70–1.49)	1.28 (0.68–2.40)	1.06 (0.55–2.02)
Heart failure	1.63 (1.16–2.29)	1.52 (1.08–2.14)	1.59 (0.91–2.77)	1.39 (0.79–2.45)
Ankle–brachial index	0.58 (0.22–1.51)	0.95 (0.36–2.49)	0.58 (0.12–2.69)	1.05 (0.22–5.00)
Statin use	0.80 (0.59–1.10)	0.82 (0.60–1.12)	0.74 (0.44–1.27)	0.76 (0.44–1.30)
ACE inhibitor use	1.23 (0.90–1.67)	1.25 (0.92–1.71)	1.48 (0.88–2.50)	1.54 (0.92–2.58)
Anti-platelet use	0.83 (0.61–1.14)	0.88 (0.64–1.21)	0.60 (0.36–1.01)	0.63 (0.37–1.07)
Median annual household income ≤\$51 249 vs median annual household income >\$51 249	1.18 (0.87–1.60)	1.16 (0.85–1.58)	1.07 (0.64–1.81)	1.04 (0.61–1.76)
Less than high school vs graduate school	1.25 (0.73–2.14)	1.15 (0.67–1.98)	1.28 (0.55–2.98)	1.14 (0.49–2.67)
High school to college vs graduate school	1.20 (0.83–1.74)	1.20 (0.83–1.74)	1.07 (0.58–2.00)	1.04 (0.56–1.95)
Six-minute walk (feet) baseline (HR calculated at unit=100 feet)	NA	0.91 (0.87–0.95)	NA	0.89 (0.83–0.96)

ACE indicates angiotensin-converting enzyme; HR, hazard ratio; NA, not available; PAD, peripheral artery disease.

statistically significant after additional adjustment for baseline 6-minute walk performance. Second, among people with PAD, depression is an independent risk factor for all-cause mortality, even after adjusting for age, sex, race, comorbidities, BMI, education, income, and smoking. However, this association was no longer significant after adjusting for baseline 6-minute walk performance.

PAD affects ≈8 million men and women in the United States and nearly 200 million men and women worldwide.<sup>25,26</sup> PAD is associated with increased rates of all-cause and cardiovascular disease mortality, compared to people without PAD.<sup>26–28</sup> PAD is also associated with greater functional impairment and more rapid functional decline compared to people without PAD.<sup>7,8,29,30</sup> We found that 19.2% of PAD participants and 12.9% of non-PAD participants met criteria for depression at baseline in our cohort. In comparison, the prevalence of depression using the Geriatric

Depression Scale, from which the GDS-S was derived, was 12% among 489 community-dwelling postmenopausal women without PAD.<sup>31</sup> Thus, the prevalence of GDS-S diagnosed depression in our non-PAD cohort was comparable to the prevalence of depression diagnosed with the full Geriatric Depression Scale in a community-dwelling cohort. The prevalence of GDS-S-diagnosed depression in our PAD cohort was higher than the prevalence of depression diagnosed with the full GDS in a community-dwelling cohort.<sup>31</sup>

Our findings are consistent with prior study in people without PAD showing that depression is more common among people with disability and that depression is associated with disability and mobility loss.<sup>32–34</sup> Similarly, PAD-related walking impairment may contribute to higher rates of new depression among people with PAD compared to those without PAD. Furthermore, the higher rate of all-cause mortality in depressed people with PAD may be explained in

**Table 4.** Adjusted Associations of Decline in the ABI During First 2 Years of Follow-Up With Subsequent Rate of Depression

	Participants With PAD (N=354)		Participants Without PAD (N=262)	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Decline in ABI >0.15 vs decline in ABI ≤0.15*	0.94 (0.31–2.86)	0.913	3.88 (1.09–13.89)	0.037
Age, y	1.02 (0.97–1.06)	0.478	1.00 (0.94–1.07)	0.941
Male sex	0.62 (0.32–1.22)	0.166	1.42 (0.53–3.81)	0.490
African American race	0.60 (0.20–1.79)	0.363	0.66 (0.19–2.36)	0.522
Six-minute walk (feet) baseline (hazard ratio calculated per 100 feet)	0.97 (0.87–1.09)	0.621	0.85 (0.76–0.97)	0.013
Body mass index, kg/m <sup>2</sup>	1.07 (1.00–1.15)	0.044	1.05 (0.97–1.13)	0.254
Current smoker	3.08 (1.39–6.80)	0.005	0.00 (0.00–∞)	0.993
Diabetes	1.37 (0.68–2.78)	0.381	0.82 (0.21–3.20)	0.771
Pulmonary disease	1.22 (0.59–2.54)	0.589	1.31 (0.51–3.36)	0.580
Cancer	2.51 (1.15–5.49)	0.021	1.25 (0.32–4.89)	0.745
Angina	0.93 (0.42–2.06)	0.861	1.54 (0.39–6.14)	0.542
Myocardial infarction	1.17 (0.53–2.61)	0.694	1.29 (0.26–6.33)	0.750
Stroke	0.61 (0.21–1.77)	0.363	0.00 (0.00–∞)	0.994
Heart failure	2.09 (0.96–4.55)	0.062	1.50 (0.34–6.59)	0.590
Hip arthritis	0.80 (0.08–7.66)	0.844	2.48 (0.26–23.31)	0.428
Knee arthritis	1.92 (0.73–5.06)	0.187	2.78 (0.90–8.57)	0.076
Disk disease	0.77 (0.37–1.57)	0.468	0.99 (0.37–2.61)	0.983
Spinal stenosis	0.39 (0.10–1.48)	0.167	1.07 (0.41–2.79)	0.886
ABI	1.22 (0.10–14.98)	0.874	3.29 (0.04–286.09)	0.602
Median annual household income ≤\$51 249 vs median annual household income >\$51 249	0.50 (0.25–1.00)	0.049	0.79 (0.29–2.16)	0.641
Less than high school vs graduate school	2.92 (0.81–10.59)	0.102	0.82 (0.15–4.35)	0.814
High school to college vs graduate school	1.80 (0.71–4.56)	0.217	0.30 (0.11–0.79)	0.015

ABI indicates Ankle–Brachial Index; PAD, peripheral artery disease.

\*Decline in the ABI during the first 2 years of follow-up was related to subsequent risk of depression.

part by poorer walking endurance among PAD patients with depressive symptoms compared to PAD patients without depressive symptoms. Poorer walking endurance, measured by the 6-minute walk, is an indicator of PAD severity and an indicator of presence and severity of multiple chronic conditions. The 6-minute walk may represent a final common pathway for the association of PAD with increased risk of depressive symptoms and for the association of depressive symptoms with increased mortality among people with PAD. However, this observational study cannot delineate causal pathways for the associations reported here. It is possible that poorer 6-minute walk performance represents psychomotor retardation associated with depression.

Among people with PAD, cross-sectional studies have documented a high prevalence of depression and poorer functional performance among depressed patients with PAD compared to nondepressed patients with PAD.<sup>2,6,35</sup> McDer-

mott et al previously reported that greater numbers of depressive symptoms, measured by the GDS-S, were associated with slower walking velocity and poorer 6-minute walk performance among 423 men and women with PAD even after adjusting for confounders including the ABI.<sup>35</sup> Smolderan et al previously reported that the prevalence of depression among 166 patients with PAD was 16%, measured by a Center for Epidemiological Studies Depression scale score ≥4, and that PAD patients with depression had poorer treadmill walking performance compared to PAD patients without depression.<sup>2</sup> In longitudinal analyses, Cherr et al studied patients with PAD undergoing lower extremity revascularization.<sup>6,36</sup> The prevalence of depression at baseline was 35%.<sup>6</sup> PAD patients undergoing lower extremity revascularization with depression at baseline had higher rates of failed revascularization, lower patency rates, and higher rates of the combined outcome of all-cause mortality and cardiovas-

**Table 5.** Adjusted Associations of Decline in the Six-Minute Walk During First 2 Years of Follow-Up With Subsequent Depression Among Participants With and Without PAD

	Participants With PAD (N=298)		Participants Without PAD (N=250)	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Decline in 6-min walk: tertile 3 vs tertile 1*	2.28 (0.96–5.45)	0.063	4.72 (1.09–20.47)	0.038
Decline in 6-min walk: tertile 2 vs tertile 1*	1.16 (0.45–2.97)	0.760	3.14 (0.70–14.06)	0.135
Age, y	1.00 (0.95–1.05)	0.914	0.98 (0.91–1.05)	0.561
Male sex	0.75 (0.35–1.59)	0.448	1.20 (0.44–3.30)	0.717
African American race	0.63 (0.18–2.24)	0.475	0.42 (0.09–2.03)	0.279
Six-minute walk (feet) baseline (hazard ratio calculated per 100 feet)	0.97 (0.86–1.11)	0.691	0.78 (0.67–0.91)	0.002
Body mass index, kg/m <sup>2</sup>	1.09 (1.00–1.19)	0.039	1.02 (0.94–1.12)	0.610
Current smoker	3.33 (1.34–8.26)	0.010	0.00 (0.00–∞)	0.995
Diabetes	1.39 (0.62–3.10)	0.419	1.32 (0.32–5.46)	0.704
Pulmonary disease	1.11 (0.48–2.55)	0.808	1.65 (0.63–4.32)	0.309
Cancer	1.94 (0.74–5.12)	0.178	1.76 (0.44–7.03)	0.427
Angina	1.04 (0.45–2.41)	0.923	2.19 (0.50–9.56)	0.295
Myocardial infarction	1.33 (0.57–3.12)	0.511	0.87 (0.15–5.02)	0.879
Stroke	1.05 (0.36–3.08)	0.934	0.00 (0.00–∞)	0.994
Heart failure	2.22 (0.94–5.21)	0.068	1.57 (0.35–7.15)	0.557
Hip arthritis	0.00 (0.00–∞)	0.991	3.48 (0.29–42.11)	0.326
Knee arthritis	1.81 (0.66–4.97)	0.249	2.44 (0.72–8.27)	0.151
Disk disease	0.93 (0.42–2.05)	0.854	0.88 (0.32–2.39)	0.799
Spinal stenosis	0.66 (0.16–2.68)	0.559	0.77 (0.27–2.19)	0.619
Ankle brachial index	0.50 (0.03–9.31)	0.643	9.61 (0.07–1357.64)	0.370
Median annual household income ≤\$51 249 vs median annual household income >\$51 249	0.53 (0.25–1.11)	0.094	0.61 (0.21–1.82)	0.380
Less than high school vs graduate school	1.51 (0.33–6.97)	0.601	0.78 (0.13–4.53)	0.781
High school to college vs graduate school	1.42 (0.52–3.91)	0.498	0.38 (0.13–1.09)	0.072

PAD indicates peripheral artery disease.

\*Tertile 1 represents the best (least) decline in the 6-minute walk between baseline and 2-year follow-up. Analyses relate change in 6-minute walk during the first 2 years of follow-up with subsequent incidence of depression.

cular disease events during follow-up compared to PAD patients undergoing revascularization without depression at baseline.<sup>6,37</sup> Depression was also associated with a higher rate of coronary heart disease events but was not associated with higher rates of all-cause mortality or cerebrovascular events, respectively.<sup>6</sup> Previous study from the Heart and Soul study of 1024 men and women with coronary artery disease demonstrated that the presence of depressive symptoms at baseline was associated with a higher incidence of PAD during follow-up in analyses adjusting for age and sex (HR=2.09, 95% CI=1.09–4.00).<sup>34</sup> However, this association was no longer significant after additional adjustment for comorbidities, PAD risk factors, medications, and health behaviors.

To our knowledge, no prior studies have compared the incidence of depression in longitudinal analyses between

people with versus without PAD. To our knowledge, no prior studies have compared all-cause or cardiovascular disease mortality rates between PAD patients with versus without depression, in a cohort of PAD participants not undergoing revascularization. Our study design does not allow us to discern potential mechanisms of our findings. However, previous study suggests that depression is associated with more adverse health behaviors, such as greater inactivity.<sup>37</sup> Prior study also suggests that depression is associated with adverse pathophysiologic changes that include increased sympathetic tone, reduced vagal tone, and immunosuppression.<sup>38–40</sup> These pathophysiologic changes may increase risk of mortality among PAD patients with depression. Further study is needed to discern the mechanisms of the associations reported here.

Our study has limitations. First, our data are observational. Results cannot be construed as causal. Second, although our findings suggest that the 6-minute walk may mediate the associations reported here, these observational data prevent the ability to delineate the causal pathway of findings reported here. Third, we used the GDS-S to measure depression. We did not collect data on clinical diagnoses of depression. However, previous study demonstrates that the GDS-S is a well-validated measure of depression.<sup>13–18</sup> Fourth, we excluded PAD participants who were wheelchair bound and those residing in a nursing home, who may have had a higher prevalence of depression than the participants included here. Our results may not be generalizable to people who did not meet our inclusion criteria. Fifth, our analyses combined data from 3 observational prospective cohorts of participants with PAD, thereby introducing heterogeneity into our analyses. We addressed heterogeneity by stratifying our analyses by study cohort and by testing for a cohort interaction for our primary analyses. Sixth, participants were identified from among patients encountered by physicians in multiple office settings in Chicago. Our findings may not be generalizable to men and women not encountered by clinicians in an office or medical center setting. Seventh, although the GDS-S is well validated in multiple settings, to our knowledge, it has not been validated against a clinical diagnosis of depression specifically in a population of patients with established cardiovascular disease.

In conclusion, people with PAD are at higher risk for developing depression compared to people without PAD. Among people with PAD, depression is associated with higher mortality rates compared to the absence of depression. Our findings suggest that clinicians should be alert to an increased incidence of depression among people with PAD. Clinicians should also be aware that the presence of depression in people with PAD is associated with increased mortality. Further study is needed to determine whether improving 6-minute walk performance can prevent depression in PAD and whether treating depression can reduce all-cause and cardiovascular disease mortality in people with PAD. Further study is also needed to delineate the mechanisms of associations reported here.

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## Disclosures

None.

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